ITEM No. 24

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FILE No. XXIV - 16

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PHARMACEUTICAL TARGETS

IN

SOUTHERN GERMANY

U/C

~~RESTRICTED~~

COMBINED INTELLIGENCE OBJECTIVES
SUB-COMMITTEE

~~RESTRICTED~~

PHARMACEUTICAL TARGETS IN SOUTHERN GERMANY

VISITED 19 to 26 MAY 1945

Reported by

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CIOS Target Numbers 24/10, 24/206, 24/252, 24/253, 24/180
Medical

COMBINED INTELLIGENCE OBJECTIVES SUB-COMMITTEE
G-2 Division, SHAEF (Rear) APO 413

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Personnel of Team

Major Thomas W. Howard, Br.
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1. Professor Doctor Walther Schoeller, Director of Research, Schering A.G., Berlin

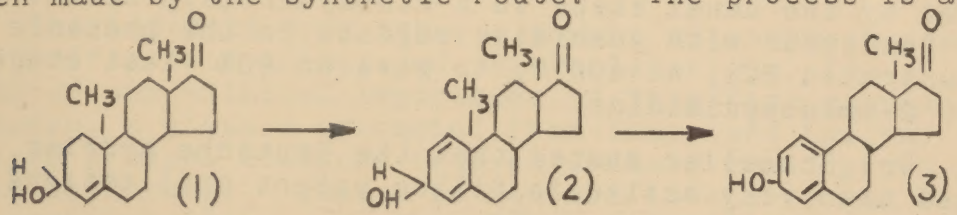
Dr. Walther Schoeller was director of research for the Schering A.G. of Berlin. He was interviewed at Allensbach (Roerenberg I) near Konstanz, where he had come for reasons of health, having left Berlin in June 1944. He had had intentions of establishing a laboratory in Bodman, nearby, but the equipment had been destroyed en route from Berlin. Consequently, he has done no work since he left Berlin. Dr. Schoeller, who is sixty-five years of age, appeared to be in poor health. He had been out of touch with his headquarters in Berlin, and had some difficulty in remembering details.

Schering Research Projects

The principal fields which interested the Schering Company during the war were as follows:

(a) Hormones

Schering A.G. had been using dehydroandrosterone (ex cholesterol) as the starting material for the manufacture of corticosterone, testosterone and progesterone. In collaboration with Dr. Inhoffen, a process for the production of estrone from the same starting material had been developed since 1939, and this synthetic route had completely replaced the production from pregnant mare's urine, of which Schering formerly used 30,000 - 50,000 litres per year. In 1944, fifteen kilos of estrone had been made by the synthetic route. The process is as follows:

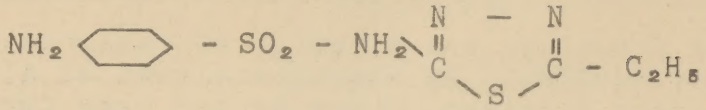


Dehydroandrosterone (1), is monobrominated and hydrogen bromide then removed to yield the diene (2). Methane is then split off by passing over a catalyst. The substance (2) is sublimed in a stream of an indifferent vapour (e.g. cyclohexane) over a catalyst (nickel or Raney nickel, etc.) at 500-600°C. This is done in an electrically wound glass tube, and a very short contact time is essential.

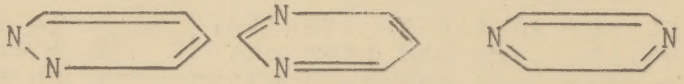
(b) Sulpha Drugs

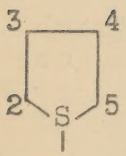
The only new sulpha drugs brought out by Schering

during the war years were stated to be Pyrimal (=Sulphadiazine), and Globucid (formula below).



Schering had filed a patent application in 1939, in Germany, Sweden and Switzerland, which covered the sulpha derivatives of amines derived from the following ring systems:





with two ring nitrogens, but Dr. Schoeller was unable to remember which particular isomer (other than the 3:4-diazine) had been covered.

Dr. Schoeller stated that Globucid had an unpleasant taste and he considered it to be less effective than sulphadiazine. It was marketed, however, because of its greater ease of manufacture. He was unable to recall the manufacturing process employed. The higher homologues of Globucid (i.e. ethyl replaced by isopropyl, butyl, etc.) were more effective with increasing chain length, and had less taste, but a higher homologue has not yet been marketed.

With regard to Pyrimal, the production was stated never to have been more than 500 kilos per month, owing to shortage of equipment. The Schering process for Pyrimal starts with acrolein purchased from Wacker, which is converted by the usual steps to B-ethoxyacrolein acetal; this is condensed with guanidine sulfate in the presence of concentrated HCl, at 400°C, to give an 80% (last stage) yield of 2-aminopyrimidine.

Dr. Schoeller stated that the Deutsche Hydrier Werke had been very active in filing patent applications for aminoheterocyclic compounds.

(c) Penicillin

Having had access to an old strain of Penicillium notatum originally sent to Germany by Fleming, Schering A.G. had attempted to obtain penicillin without success. Studies to find an active strain have since been in progress, so far without apparent success. Based on an early Heilbron formula ($C_{24}H_{36}O_{11}N$) for penicillin, Schoeller had an erroneous idea that penicillin might be built up from glucosamine ($C_6H_{12}O_5N$) and glauconic acid ($C_8H_{24}O_6$).

(d) Miscellaneous

Unsuccessful attempts were made to synthesize

Dr. Schoeller, in collaboration with Professor Warburg, had been interested in cancer for twenty years, but apparently this had so far led to no important results.

Gesarol (D.D.T.) was being produced under license in large quantities by Schering, but no research improvements had been made.

2. Luitpold-Werk, Munich 25, Thalkirchen, Zielstatt Strasse 9, 13-15

The Luitpold-Werk is situated at Thalkirchen, a suburb to the west of Munich. The factory was inspected, and the director Walther Karreth (son of the founder, August Karreth, who was recently deceased) was interrogated at his home at Wolfratshauserstrasse 32A, Thalkirchen.

The Luitpold-Werk is a small factory, covering about an acre of land, and consists of two medium-sized manufacturing buildings. In normal times it employed 4 chemists and 1 pharmacist in addition to the director who was himself a chemist and pharmacist, and about 170 workpeople, the bulk of the latter being women employed in ampouling, tableting, packaging, etc. The workpeople included about 50 directed Jews, 6 French, 20 Russian, 12 Polish and 12 Ukrainian workers. The factory had been partially destroyed by air attack in September, 1943, and further damaged in November 1944, and is not at present in a working condition.

The Luitpold-Werk makes a number of enzyme preparations and extracts of animal and vegetable origin, few of which seem of any clinical importance. This firm manufactures Clauden, a styptic extracted from lung, and Luizym, an enzyme product obtained from an unnamed mould grown on a bran substrate. Luizym is claimed to aid in the digestion of carbohydrates. Another product, Monotrean, which is made by the same firm, is a mixture of papaverine and quinine, and is claimed to be of value in treating vertigo. For this and other preparations, approximately 30 kilo of quinine per month were used, supplies of which were said to have been freely obtainable throughout from the central state pool in Berlin.

The total sales turnover of the Luitpold-werk was stated to have been approximately 1½ million marks in 1939, but to have fallen very appreciably in recent years.

This target is of little importance and no further investigation is recommended.

3. Alpine Chemische A.G., Kufstein, Austria

The plant is located on the railroad about 4 kilometers south of Kufstein, which is 97 kilometers southeast of Munich, and just across the Austrian border.

The plant was not appreciably damaged by air raids, and had operated regularly until 2 months prior to our visit.

This plant is on the same site and under the same management as Elchemie G.m.b.H., which manufactures hydrogen peroxide. Alpine, which is the pharmaceutical division, occupies four main buildings of moderate size. The combined sales of Alpine and Elchemie were stated to be about 4 million marks per year, of which pharmaceuticals represented less than half.

The two related companies have about 240 employees, of which 205 are in the Alpine Chemische A.G. division. The technical personnel of the latter consisted of 5 chemists, 1 bacteriologist and 1 so-called pharmacologist.

It was founded in 1921 as a factory for the production of salicylic acid and sodium salicylate, and is owned by the Schering Company, which uses it as a marketing outlet for some of its less scientific items. Production has increased somewhat during the war. It shares the production of a number of items with another Schering subsidiary, namely, Chemische Fabrik Aubing, G.m.b.H., located at Aubing, Germany.

The Chairman of the Board is Dr. Birchmeyer of Berlin; the Vice-Chairman is Dr. W. Zeiss, the former general director of Schering in Berlin, who now lives on the Austrian frontier between Bayerischzell and Thiersee. The manager of the organization was Dr. Elleder, who is still employed there, but was superseded on 8 May 1945 by Dr. L. Knop, a Jugoslav, at the instigation of the Austrian resistance movement. Knop had been employed by the firm for three years as a chemist. He also manages the peroxide plant. Dr. K. v. Brentano is the scientific director and perhaps represents the Schering headquarters' interests. At the time of our visit, all the executives and their families were living in the factory, and a prisoner of war camp for Germans was located on the factory grounds.

On interrogation, Dr. Weiss said that Alpine was the largest chemical factory in Vorarlberg and Tyrol, and that it was placed there to help industrialize Austria. As Zeiss had been living here since 1939, he was not too well informed regarding more recent developments of Schering.

On the manufacturing side, the Alpine Chemische A.G. is mainly concerned with the mixing and packaging of pharmaceutical products. The only synthetic operations carried out are the manufacture of salicylic acid from phenol by the Kolbe process, purification by sublimation, and manufacture of pure sodium salicylate (double aqueous crystallization process). The bulk of the salicylic acid is dispatched to the Schering A.G. factory at Aubing for conversion to aspirin.

The activities of the Alpine Chemische A.G. are summarized in the following table:

	Product	Nature	Indications	Manufacturing Operations done by Alpine Works	Approximate Annual Quantity
	Salicylic acid, tech.			Manufacture from phenol; 90.7% yield	100 tons
	Salicylic acid, pure			Purification by sublimation; 96.7% yield	350 tons
1	Mirion	Iodized Hexamine	Arthritis deformans; Syphilis; Gonorrhea complications	Packaging	Manufacture stopped due to lack of sales
2	Ovis (trademark)	Solution of Hexylresorcin, Benzoin, and Salicylic acid in alcohol	Athlete's foot	Mixing and Packing	1/2 ton Hexylresorcin
3	Artamin	Cinchophen	Gout, etc.	Tableting - granule supplied ex Schering Berlin	3.5 tons
4	Favorin (trademark)	Benzyl benzoate 35% Triethanolamine 50% Benzyl alcohol 17%	Scabies	Mixing and bottling	36 tons
5	Degewop Insulin	Insulin	Diabetes	Material supplied by Schering. Solution and ampouling (testing done in Berlin)	
6	Degewop-Neo Insulin	Zinc Insulin	"	"	
7	Degewop P.Z. Insulin	Protamine zinc insulin	"	"	
8	Pernaemyl einfach	Liver extract	Anaemia	"	
9	Pernaemyl forte	Concentrated liver extract	"	"	

Products 1-4 incl. were specialities of the Alpine Chemische A.G., and were sold under their own label.

Products 5-9 incl. were sold through the firm of Degewop (Deutsch Gesellschaft für Wissenschaftliche Organ-Präparate), an associate of the Schering organization.

In addition to the above, Alpine Chemische A.G. carried stocks of the following Schering products in finished, packaged form. They had tableted Atophan and Albucid from granules supplied by Schering of Berlin, and apparently assisted on occasion in the final pharmaceutical and packaging operations of some of the other products.

Albucid	Cyclotropin
Arcanol	Neotropin
Arthegon	Neutralon
Atophan	Progynon
Atophanyl	Proluton
Cortiron	Testoviron
	Urotropin

They had tableted experimentally a small quantity of the new Schering sulphonamide, Globucid (p-aminobenzenesulphonamide-ethyl-thiodiazol), and sample tablets were taken.

Sera and vaccines were produced on a very limited and primitive scale.

4. Chemische Fabrik Aubing, G.m.b.H., at Aubing, near Munich

This company is located at Aubing, about 10 kilometers west of Munich, on a tract of land measuring 4700 sq. meters, of which 500 sq. meters are occupied by buildings. The plant is practically undamaged, and operated full scale until 28 April, two days before the arrival of U.S. troops. It has adequate supplies to continue operations for 4 to 6 weeks, but lacks coal.

The company was founded in 1905 by Dr. Moritz Bloch, who died in the United States in 1943. His son, Dr. Kurt Bloch, was also connected with the firm until the anti-Semitic policy forced him and his father to relinquish control to the elder Bloch's brother-in-law, Dr. Hermann Sorge, who is still with the company.

Ownership of the company is divided equally between

Schering and Heyl A.G. The plant manager is Dr. Ing. Siegfried Balke, a well informed and cooperative man about 50 years old. Dr. Sorge, already mentioned, together with Balke and one other chemist, share the research work that is done, which is not extensive. The company normally employs about 100 persons, and before the end of the war, 40 of these were foreigners, mainly Ukrainians, who were said to be very satisfactory workers. They now have a total personnel of about 30 Germans.

By order of the government, such personnel was required, during the last year or so, to work 72 hours per week. This plant operated on a 5 day per week schedule, over 14 hours per day. Labor was paid overtime about 48 hours per week. Their regular pay rate was about 80 pf. per hour.

Chemische Fabrik Aubing manufactures the following synthetic products:

Product	Quantity made in 1944	Notes
Acetylsalicylic acid	210 tons	
Salicylic acid (tech.), Phenacetin	16 tons 85 tons	Recovered ex aspirin manufacture. Claimed to be sole manufacturer in Europe, with exception of I.G.
Salol	35 tons	Also made by Heyden and I.G.
Acetanilid (tech.)	135 tons	Sole manufacturers in Germany, outside I.G.; Aubing sells to the sulpha drug manufacturers.
Sulphonal	0.6 tons	Sole manufacturers in Europe.
Methylsulphonal	0.8 tons	Sole manufacturers in Europe.
Lactylphenetidine	2 tons	Also made by I.G.
Acetanilid pure	15 3/4 tons	
Veterinary products	6 tons	Mainly mixing.

The manufacturing processes employed are described briefly below.

Acetylsalicylic acid

Salicylic acid (ex. Alpine Chemische Werk, Kufstein) and 5% excess of acetic anhydride (ex. Wacker) are reacted

in an aluminum autoclave. The reaction mass is thinned by addition of petrol, and the product filtered on a centrifuge. Pure acetic acid is recovered from the filtrate by vacuum distillation. The crude aspirin is recrystallized from petrol, acetic acid, or alcohol, according to the type of crystal required. The mother liquors from the crystallization are distilled to recover solvent and the residue hydrolized to recover crude salicylic acid, which is sold as such and not re-processed.

Yield: 80-82% of theory on salicylic acid charged.
Recovery: Approx. 15% of tech. salicylic acid.

Phenacetin

Preparation of p-Phenetidine

p-chloronitrobenzene (ex. I.-G.) was reacted with 5 mol. ethanol and 1 mol. KOH in a C.I. vessel, finely divided, dry MnO_2 (ex Sulphonal process) being added as catalyst. The reaction mixture is heated at a rate of $1^{\circ}C$ per hour from $20^{\circ}C$ to $60^{\circ}C$, and then somewhat more rapidly to $80^{\circ}C$. The solution is filter-pressed, and distilled to remove excess ethanol. The crude p-nitrophenetole is used directly for the next stage.

The above reaction conditions, which were worked out at Aubing and not patented, have been used since 1932.

The mother nitro compound is run into hot aqueous Na_2S_2 solution, and the phenetidine extracted with benzene. Benzene is distilled off and the product vacuum distilled. The yield of p-phenetidine is 92-93% theory on p-chloronitrobenzene.

Acetylation

This is done in an aluminum autoclave, using glacial acetic acid (ca.20% excess), and working at $130^{\circ}C$ under 3 atmos. pressure. Aqueous acetic acid is distilled off in vacuum and sent for concentration. The product is purified by distillation at 10-15 mm. pressure, followed by recrystallization first from a mixture of benzene (80%) and ethanol (20%), and then from ethanol if necessary.

Yield of phenacetin, 76-78% of theory overall on p-chloronitrobenzene.

Salol

100 kg. of technical salicylic acid (ex Alpine Works,

or as recovered from aspirin manufacture), 75 kg. of phenol and 53 kg. of $POCl_3$ are refluxed at 110°-115°C in a silver lined (1 mm) copper vessel. Total reaction time 4-5 hours. The molten product is separated from the phosphoric acid layer, granulated by drowning into water, dried by melting and distilled at 4-5 mm. pressure in all copper equipment.

Yield: No figure was obtained.

Acetanilid

Aniline (ex I.G.) is reacted with acetic acid in a 300 gal. aluminum autoclave under 3 atmos. pressure. Excess acetic acid is removed by vacuum distillation, and the product purified to technical grade by vacuum distillations.

Yield: Practically quantitative.

Medicinal quality acetanilid is made by recrystallization from ethanol.

Yield: 90% of theory overall on aniline.

Sulphonal and Methylsulphonal

Sodium ethyl sulphate

An excess of ethanol (90-95 alcohol content) is added to oleum (25% SO_3). Soda ash is added to neutralize and alcohol removed by distillation. The residual mixture of sodium sulphate and sodium ethyl sulphate is used for the next stage.

"Mercaptol"

The crude sodium ethyl sulphate is reacted in a copper vessel with 35% sodium hydrogen sulphide solution. The quantity of ethyl mercaptan in the reaction pan is estimated. It is then distilled into the calculated equivalent quantity of acetone (for sulphonal manufacture) or methylethylketone (for methylsulphonal) which has been mixed with conc. H_2SO_4. After reaction water is added and the mercaptol separated from the aqueous sulphonic and layer. It was explained that the mother liquors are disposed of by running directly into the chalk subsoil.

Yield of "mercaptol": 52 kilos from 45 kilos ethyl mercaptan.

Oxidation

15 kilos of "mercaptol" are dissolved in benzene, water added, and the mixture stewed vigorously in a 400 gal. wooden vat. $KMnO_4$ crystals are added to the emulsion until an excess is present, 50-55 kilo $KMnO_4$ being required. MnO_2 is removed by filter-pressing (part of this recovery after drying is used on the p-nitrophenetole process), the benzene solution is separated and benzene then removed by distillation. The residue of crude sulphonal (or methylsulphonal) is purified by crystallization from a) water and b) ethanol.

Yield: 11-12 Kg. Sulphonal, and some second crops which are re-worked.

Lactylphenetidine

Equimolecular proportions of phenetidine and 100% liquid lactic acid are reacted at 140°C in an aluminum vessel until evolution of water ceases (3-4 hours).

The product is purified by crystallization from ethanol.

Yield: 60-70% on phenetidine.

Nicotinic Acid

Plans were in hand to make nicotinic acid, and equipment for acidising from 8-hydroxyquinoline (purchased from Vanillin Fabrik, Hamburg) by nitric acid or potassium permanganate was on site but had not been erected. The estimated production is 100 kg. per month, at an expected cost of 100 marks per kilo.

Veterinary Products

The company produces a small number of such items in quite limited volume. One series, called "Serapis", used against liver flukes in sheep and cattle, contains as active ingredients, CCl_4 for sheep and hexachlorethane or a mixture of trichlorethane and pentachlorethane for cows. Tetrachlorethylene does not seem to be used in Germany. "Dalbeen" is an injectable solution of casein, MnO_2, and mono- and di-iodosalicylic acid for infectious diseases.

Pharmaceutical Products, Human

None of these are outstanding. The company made tablets of aspirin, etc. for export and on private formula for other firms, as well as a limited number of ointments. They operate 3 triple-punch and 1 rotary tablet machines.

5. F. Hoffman-La Roche & Co. A.G. at Grenzach

This is an excellently laid out plant, completely undamaged, covering 6 hectares or a 16 hectare site. A number of the buildings, notably those for producing Vitamin C, have been erected and well equipped during the war.

The managing director, Dr. Waldemar Hellmich, and the assistant director, Dipl. Ing. Hugo Fischer, were interrogated, and freely provided information. Dr. Hellmich said that in spite of pressure he had refused to become a member of the Nazi party.

The direction of the company is in the hands of a board of four persons in Basel, of whom Dr. Gsell is chiefly concerned with this plant. The capital of 4 million marks was certified to be entirely in Swiss hands. This branch of the firm is registered in Berlin.

The firm depends on the parent company in Basel for all its research and development work and for the final analytical control. This company sells to the trade only in Germany but delivers some bulk materials to the parent company, which does not sell in Germany except through the German firm.

Before the war the turnover was of the order of 6 million marks per annum, and rose in 1944 to 22 million marks, due principally to Vitamin C production. There is an arrangement whereby 15% of the turnover is paid to the Swiss company.

This company has had very little to do with the Roche organizations in Great Britain or the United States.

The firm has normally about 650 employees of which about 120 are salaried staff. At present the payroll has fallen to about 450. There are 8 process chemists and 1 analyst.

The normal working week is 48 hours, and is paid for at the rate of about 75 pfg. per hour for men and 55 pfg. for women. Overtime is paid at 25% over the basic hourly rate. During the War they have been working a 55-60 hour week on a single day shift.

Factory Operations

Heat and Power

Electricity was bought. About 1,400,000 KHW were used

per annum. Their own boiler plant consumed about 5000 tons of coal per annum and produced about 43,000 tons of steam, most of which is used for manufacturing purposes.

Production in 1944

Allional	4,224.-	kg.
Allylalkohol	3,572.5	
Allylisopropylbarbitursäure	4,825.-	
Arsylen natrium	153.-	
Ascorbinsäure	59,235.4	
Barbitursaures Natrium	2,813.-	
Cyanacetamid	3,401.-	
Cyanaethylester	5,680.-	
Diaethylamin	613.-	
Diaethylbarbitursäure	8,854.-	
Dimethylhydrochinon	70.-	
Dimethylhydrochinon-aldehyd	635.-	
Guajacol	43,850.-	
Histidin	398.9	
Isacen	634.8	
Isopropylantipyrin	1,676.-	
Kaliumsulfoguajacolicum	57,550.-	
Larocain	261.8	
Larosan	34,848.-	
Lösungen	339,106.-	
Morphium aus Mohn	435.-	
Morphium aus Opium	2,773.-	
Papaverin synth.	1,374.-	
Phenolphthalein	36,557.-	
Phenylhydrazin	2,806.-	
Phytol	9.-	
Prostigminbromid	38.6	
Syntropanphosphat	103.4	
Tablettenanlage	366.6	Mill.
Tocopherolacetat	18.6	
Vanillin	15,691.5	

Processes

The detailed chemical procedures for the manufacture of the following products were obtained:

Verfahren:	Larocain "Roche" aus Nitrochlorhydrat Akt. Z.: L IX,1 vom 19.Juli 1939 (Abschr.)
Verfahren:	Nitrochlorhydrat aus Aminoalkohol Akt. Z.: N VII,1 vom 6.Juli 1939 (Abschr.)
Int.Verf.:	Thyroxin Akt.Z.: Nr.292 vom 28.Sept.1939(Orig.Nr.3)
Verfahren:	Scopolamin aus Datura metel und Datura stramonium vom 30.Juni 1932 (Ex.Nr.3)

Int.Verf.: Ameisensäure-methylester
Akt.Z.Nr.295 vom 6.Dez.1939 (Abschr.)
Int.Verf.: Phenylessigsäure-acethylester
Akt.Z.: Nr.296 vom 7.Dez.1939 (Abschr.)
Int.Verf.: Tropasäure-aethylester
Akt.Z.Nr. 297 vom 7.Dez.1939 (Abschr.)
Verfahren: Tropasaures Kalium aus Tropasäureäethylester
Syntropansynthese Stufe F
Akt.Z. T XV,1 vom 21.Aug.1935 (Abschr.)
Verfahren: Aminochlorid Syntropansynthese Stufe B
Akt.Z.: A XXII,1 vom 20.8.1935 (Abschr.)
Verfahren: Syntropan-Phosphat Syntropansynthese Stufe
G Akt.Z. S XXXI,1 v.27.Okt.1937 (Abschr.)
Verfahren: Kalium sulfoguajacolic.
vom. 15.3.1927 Ex.Nr.2
Verfahren: Guajacol aus o-Anisidin ohne Datum
Verfahren: Sedormid, kleine Ansätze
Akt.Z.: S XXXII, 1 vom 12.Juni 1936
(Abschr.1)
Verfahren: Prostigmin-Ampullenlösung
Akt.Z.: P XV, 2 vom 30.Sept.1932 (Orig.Nr.5)
Verfahren: Pituglandol ohne Datum
Verfahren: Ovoglandol für Ampullen
vom 3.Juni 1932
Int.Verf.: Oestroglandol-Ampullenlösung "Roche" 1000
I.E. Akt.Z.: Nr. 190 vom 6.3.1936
(Orig.Nr.3)

It was stressed by Dr. Hellmich that these processes were the property of the Swiss company.

In addition to the above, chemical manufactures there is a pharmaceutical department for the preparation of prescriptions, galenicals, tablets, ampoules, etc.

The only important addition to their normal range of manufactures during the war was Vitamin C.